

## REMARKS

### FORMAL MATTERS

Claims 48-56, 58-67, 69-72, 74-81 and 83-91 are pending and currently under examination after entry of the amendments set forth herein.

Claims 48-56, 58-67, 69-72, 74-81, 83-94 and 96-99 were rejected.

Claims 92-94 and 96-99 are canceled herein without prejudice to renewal.

Claims 48, 56, 63-65, 67, 69-72, 81 and 84-86 are amended. Support for these amendments can be found throughout the application as originally filed and in the following exemplary locations: page 5, lines 17-22; page 10, lines 21-25; and Examples 1-5.

No new matter is added.

### REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

#### *Enablement*

Claims 48-56, 58-67, 69-72, 74-81, and 83-91 were rejected as allegedly failing to comply with the enablement requirement of 35 U.S.C. §112, first paragraph. Applicants respectfully traverse the rejection as discussed below.

Applicants burden under §112, first paragraph, is to provide a disclosure containing sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The test for enablement asks whether one reasonably skilled in the art could make or use the recited invention from the disclosures of the patent application coupled with information known in the art—without having to resort to undue experimentation. *United States v. Electronics*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). In addition, a patent specification need not teach, and preferably omits, what is well known in the art. See, e.g., *In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) and *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987).

As best understood by the Applicants, it is the position of the Office that the specification is enabling for sufentanil as a fentanyl congener, but does not reasonably provide enablement for fentanyl itself or any other fentanyl congener. Specifically, the Office states that “*The present specification enabled sufentanil implantable devices that provides specific delivery rate of sufentanil.*” Office Action dated June 2, 2009, page 9.

Applicants respectfully submit that the claims as presented in the response filed March 19, 2009 were fully enabled as discussed therein. However, solely in the interest of expediting prosecution of the

instant application, Applicants have amended independent claims 48, 63 and 84 to recite that the composition comprises “sufentanil.”

In view of the above, Applicants respectfully request withdrawal of the rejection of claims 48-56, 58-67, 69-72, 74-81, and 83-91 under §112, first paragraph.

#### **REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH**

Claims 56, 67 and 81 were rejected under 35 U.S.C. §112, second paragraph, because the term “at least about” allegedly renders the claims indefinite.

Applicants respectfully submit that the claims are clear in view of the specification as filed. However, solely in the interest of expediting prosecution of the instant application, Applicants have amended claims 56, 67 and 81 such that they do not recite the term “at least about.”

In view of the above, Applicants respectfully request withdrawal of the rejection of claims 56, 67 and 81 under §112, second paragraph.

#### **REJECTIONS UNDER 35 U.S.C. §103(a)**

Claims 48-56, 58-67, 69-72, 74-81, and 83-91 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over the article “Analgesia and Sedation with Sufentanil in Intensive Care Medicine” by Wappler et al.<sup>1</sup> (henceforth “Wappler”) in view of the articles “Long-Term Spinal Opioid Therapy in Terminally Ill Cancer Pain Patients” by Wagemans et al. (henceforth “Wagemans”), Peterson et al. (U.S. 6,524,305) (henceforth “Peterson”), and Nelson et al. (U.S. 5,980,927) (henceforth “Nelson”). Applicants respectfully traverse the rejection as discussed below.

In order to meet its burden in establishing a rejection under 35 U.S.C. §103 the Office must first demonstrate that the combined prior art references teach or suggest all the claimed limitations.<sup>2</sup> Furthermore, as indicated by the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, it will often be necessary “to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue.”<sup>3</sup> “This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations

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<sup>1</sup> Applicants note that the rejection refers to the English translation of the article “Level Concept of Analgesic Dosing in Intensive Care Medicine with Sufentanil” *Anästhesiol Intensivmed Notfallmed Schmerzther* (1998) 33(1):8-26, by Wappler et al.

<sup>2</sup> See *Pharmasset Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342 (Fed. Cir. 2007)

<sup>3</sup> *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007).

of what, in some sense, is already known.”<sup>4</sup> Finally, in *KSR* the Court held “[w]hen the prior art teaches away from combining certain known elements, discovery of successful means of combining them is more likely to be nonobvious.”<sup>5</sup>

*The Proposed Combination Fails to Teach or Suggest Each and Every Claim Element*

The methods of independent claims 48 and 63 as currently amended each require systemically administering a composition comprising sufentanil to a subject, *wherein the sufentanil is present in the composition at a concentration of about 0.5 mg/ml to about 500 mg/ml*. Applicants respectfully submit that the combination of Wappler, Wagemans, Peterson and Nelson fails to teach or suggest at least this element of claims 48, 63, and the claims which depend therefrom.

In an attempt to establish the rejection, the Office argues that:<sup>6</sup>

- At the time of the invention, it was well known to administer sufentanil in a continuous manner at a daily dose of 98-3600 µg/day, i.e. 0.098 to 3.6 mg/day, to induce analgesia as taught by Wappler.
- It was further known that sufentanil is the preferred analgesic for long-term opioid therapy and can be administered in the minimal effective dose for months or years by implantable pumps as taught by Wagemans.
- Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide systemic analgesia using sufentanil delivered continuously at concentration of 4.5 µg/hr to 150 µg/hr, i.e. 98-3600 µg/day, as disclosed by Wappler and deliver sufentanil using implantable infusion pump disclosed by Wagemans.<sup>7</sup>

The Office acknowledges at page 14 of the instant Office Action that Wappler does not teach delivery of sufentanil using implantable convective devices that deliver from 0.01 µl/day to 2ml/day to provide analgesia for prolonged periods. The Office asserts that this missing teaching is supplied by Peterson. Finally, the Office relies on Nelson for an alleged teaching that loading dose sufficient for long periods of administration can be calculated if the daily dose is known. According to the Office, Nelson teaches a daily dose of sufentanil that is 0.1 to 0.3 mg/day.

The only weight-based delivery rates relied on by the Office are provided in Wappler and Nelson. However, when these references are examined closely for the alleged teachings it is clear that they fail, both individually and in combination, to teach a composition comprising sufentanil “*wherein the*

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<sup>4</sup> *Id.* at 1741.

<sup>5</sup> *Id.* at 1740.

<sup>6</sup> Office Action mailed 6/2/2009, page 15.

<sup>7</sup> Applicants note that 4.5 µg/hr = 108 µg/day (not 98 µg/day as suggested by the Office).

*sufentanil is present in the composition at a concentration of about 0.5 mg/ml to about 500 mg/ml*" as required by independent claims 48 and 63.

Even if Wappler's alleged teaching of "98-3600 µg/day, i.e. 0.098 to 3.6 mg/day" is considered for the sake of argument,<sup>8</sup> such a teaching does not amount to a teaching to administer a composition having the concentration range set forth in the claims. In other words, a teaching to deliver 0.098 to 3.6 mg/day of sufentanil tells one of ordinary skill in the art nothing about the concentration (in mg/ml) of sufentanil in the composition.

Nelson does not remedy the deficiencies in Wappler with respect to the claimed concentration of sufentanil in the composition. According to the Office, "Table 1 of the reference teaches that loading dose sufficient for long period administration, e.g., six month dose, can be calculated if the daily dose is known. Nelson teaches the daily dose of sufentanil is 0.1 to 0.3 mg/day (col.6, lines 26-31)."<sup>9</sup>

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<sup>8</sup> Applicants in no way acknowledge that Wappler in fact teaches such a delivery rate.

<sup>9</sup> Office Action mailed 6/2/2009, page 15.

Table 1 of Nelson along with col. 6, lines 26-31 are provided below for reference (emphasis added).

Table 1 shown hereinbelow provides an example of the device size requirements for providing a minimal six-month dose of fentanyl to accomplish chronic pain control in a more or less typical situation involving intrathecal administration.

TABLE I

DRUG NEEDS

Intrathecal fentanyl dosage: 0.1 to 0.3 mg/day

Using minimal dose for 6 months

Assuming polymer and drug densities = 1 g/cm<sup>3</sup> or 1 mg/mm<sup>3</sup>  
0.1 mg/day × 180 days × 1 mm<sup>3</sup>/mg = 18.0 mm<sup>3</sup> fentanyl to be delivered  
DEVICE SIZE

Assume 20% loading, and 50% delivery in 6 months

$\frac{1.80 \text{ mm}^3 \text{ of active fentanyl}}{0.1 \text{ mm}^3 \text{ actives/mm}^3 \text{ inactives}} = 180.0 \text{ mm}^3 \text{ of device}$

Device of volume 180.0 mm<sup>3</sup> or 0.18 cm<sup>3</sup>:

Cube, 0.56 cm on-a-side  
Cylinder, D = 1.8 mm, L = 70 mm (2.8 in)

It should be immediately clear from the above that Nelson does not provide the teaching suggested by the Office. Instead, the cited portions of Nelson relied on by the Office clearly refer to fentanyl and a fentanyl dosage and not to sufentanil or a sufentanil dosage. Accordingly, Nelson cannot cure the deficiencies in Wappler with respect to the claimed concentration of sufentanil in the composition. As neither Wagemans nor Peterson disclose any specific sufentanil concentrations, these references also fail to cure the identified deficiencies in Wappler.

In view of the above, Applicants submit that the combination of Wappler, Wagemans, Peterson and Nelson fails to teach or suggest each and every element of independent claims 48 and 63 and those dependent claims which depend ultimately therefrom. Accordingly, the Office has failed to establish a *prima facie* case of obviousness with respect to these claims.

*No Apparent Reason to Combine Wappler and Wagemans*

Applicants respectfully submit that there would have been no apparent reason for one of ordinary skill in the art to combine the disclosed delivery rates of Wappler in the continuous infusion method described by Wagemans. This is because Wagemans solves the problem of providing analgesia in a subject in a completely different manner than that employed by Wappler.

Specifically, Wagemans describes spinal, i.e., **local administration** of opioids. Wagemans teaches that an advantage of spinal administration is that opioids act directly at the spinal cord level by binding to specific opioid receptors in the dorsal horn of the spinal cord.<sup>10</sup> Thus, the opioid, e.g., sufentanil, is delivered directly to the receptors it will act upon. Accordingly, Wagemans states: “The normal dosage of spinal opioids is considerably lower than systemic opioid dosage, therefore producing fewer side effects.”<sup>11</sup> Thus, Wagemans does not teach or suggest systemic administration of sufentanil as currently claimed, because to do so would defeat Wagemans stated purpose of providing analgesia via local administration to the spine.

Wagemans indicates that in epidural administration “systemic adsorption” occurs in addition to penetration of the dura matter and arachnoid. However, Wagemans clearly teaches that epidural administration is **local administration** in the context of opioid delivery. By way of example, Wagemans indicates that the advantages of spinal administration (e.g., epidural administration) include “the ability to reach higher concentrations of opioids at the receptor site *when compared with systemic administration*.<sup>12</sup>

In contrast, Wappler does not describe the local administration of opioids to the spine. Wappler does not explicitly indicate the route of administration used. However, Wappler does suggest that the drug is administered *intravenously*, i.e., systemically. Specifically, Wappler indicates that “some authors recommend the continuous giving of the drugs via *syringe pumps*.<sup>13</sup> As an example, Wappler refers to reference no. 1, which is an article entitled “*Analgesia and Sedation in Intensive Care*” by Aitkenhead, A.R. *Br. F. Anaesth.* (1989) 63:196-206. Aitkenhead describes its method of administration as follows:<sup>14</sup>

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<sup>10</sup> Wagemans page 71, left column.

<sup>11</sup> *Id.* (emphasis added).

<sup>12</sup> *Id.* (emphasis added).

<sup>13</sup> See the second paragraph of the Introduction in the translation of the full text Wappler et al. document (provided with the RCE filed Aug. 26, 2008) (emphasis added).

<sup>14</sup> Aitkenhead *Br. F. Anaesth.* (1989) 63:196-206, page 198 (provided previously).

#### METHOD OF ADMINISTRATION

Most sedative and analgesic drugs are administered parenterally in the ICU. Sedation is achieved most satisfactorily by continuous i.v. infusion, a technique which avoids the peaks and troughs of analgesia and sedation associated with the use of intermittent i.m. or i.v. administration. The rate of infusion should be tailored to the patient's requirements, and usually requires adjustment from time to time. It is usually preferable to initiate sedation with a relatively rapid infusion, rather than by a bolus dose which may result in undesirable cardiovascular depression.

Thus, the reference cited by Wappler as showing continuous administration via "syringe pump" is a reference in which the administration is by continuous i.v. infusion. Wappler goes on to describe its method of administration as one which utilizes a "syringe pump."<sup>15</sup> Furthermore, in discussing their results in the context of previous studies, Wappler et al. specifically refers to references in which sufentanil was administered *intravenously*. See, for example, the second paragraph of the Discussion section in Wappler, wherein Bailey et al. (1990) *Anesth. Analg.* 70:8-15 is cited and described. Bailey et al. describe their administration as follows:<sup>16</sup>

The magnitude and duration of analgesia and respiratory depression induced by fentanyl (1.0, 2.0, and 4.0 micrograms/kg) and sufentanil (0.1, 0.2, and 0.4 microgram/kg) after intravenous administration over 30 s were measured in 30 healthy young adult male volunteers divided into three groups and studied in a double-blind, randomized fashion. Each volunteer received one dose of fentanyl or sufentanil and no sooner than 48 h later, the corresponding equipotent dose of the other opioid.

In view of the above, Wappler suggests intravenous systemic administration rather than local spinal delivery as described in Wagemans.

As evidenced by Wagemans, one of ordinary skill in the art would not apply a dosage of sufentanil suitable for intravenous administration in the context of local spinal administration because in local spinal administration the sufentanil is delivered directly to the receptors it will act upon. Thus, one

<sup>15</sup> See page 3 of the English translation of the full text Wappler et al. document (provided with the RCE filed Aug. 26, 2008).

<sup>16</sup> Bailey et al. (1990) *Anesth. Analg.* 70:8-15 (Provided previously).

of ordinary skill in the art would have no apparent reason to apply the dosage regime for systemic administration of Wappler in the context of the local spinal administration described by Wagemans.

As discussed above, the Office bases its §103 rejection on a combination including both Wappler and Wagemans. Applicants submit that since there is no apparent reason to combine the teachings of these two references, a *prima facie* case of obviousness has not been established with respect to any of the rejected claims.

*Nelson Teaches Away from the Combination with Wappler and Teaches Away from the Claimed Invention*

Nelson solves the problem of providing analgesia in a subject in a completely different manner than that employed by Wappler. Rather than administering a drug systemically as suggested in Wappler, Nelson provides a device and method for administering an analgesic directly to the neuraxis of an organism.

Nelson states that “[t]he current regimen for treatment of these patients is systemic administration of relatively high doses of analgesics by for example oral, subcutaneous, intramuscular, intravenous and related routes on a daily or continuous basis.” Nelson goes on to describe problems associated with various methods of systemic administration of opioid analgesics. See, for example, Nelson at column 1, lines 28-49. Finally, Nelson indicates that “[t]he present invention provides an alternative means for achieving continuous central nervous system administration of an analgesic into the neuraxis via intraventricular, epidural, intrathecal and related routes for those suffering chronic pain and is directed to solving one or more of the problems noted above.”

By describing the various problems associated with systemic administration of opioid analgesics, and by offering its own device and method as an alternative, Nelson clearly teaches away from the systemic administration of opioid analgesics such as sufentanil. In direct contrast to Nelson, Wappler suggests systemic administration of drug as discussed above.

In short: Wappler points the ordinarily skilled artisan towards the systemic administration of opioids. Nelson states a goal of avoiding systemic administration, and provides a method to accomplish delivery directly to the central nervous system. As such, one of ordinary skill in the art would be directed away from the combination with Wappler given Nelson’s teaching that the systemic administration of these analgesics is undesirable.

Furthermore, the claims as currently amended specifically recite “systemically administering” a composition. As such, Nelson, which teaches away from the systemic administration of opioids, teaches away from the claimed invention. The Office cannot look to Nelson for an alleged teaching that a loading dose sufficient for long periods of administration can be calculated if the daily dose is known without also considering those portions of Nelson which teach away from the proposed combination and the claimed invention.

In view of the above, Applicants respectfully submit that the Office has failed to provide a *prima facie* case of obviousness with respect to any of the rejected claims. Reconsideration and withdrawal of the rejection are respectfully requested.

**CONCLUSION**

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number DURE-007CON2.

Respectfully submitted,  
BOZICEVIC, FIELD & FRANCIS LLP

Date: November 30, 2009 By: /Michael B. Rubin, Reg. No. 61,231/  
Michael B. Rubin  
Registration No. 61,231

Date: November 30, 2009 By: /Carol L. Francis, Reg. No. 36,513/  
Carol L. Francis, Ph.D.  
Registration No. 36,513

BOZICEVIC, FIELD & FRANCIS LLP  
1900 University Avenue, Suite 200  
East Palo Alto, California 94303  
Telephone: (650) 327-3400  
Facsimile: (650) 327-3231